Platelet-Mediated Thrombosis and Drug-Eluting Stents

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Stent thrombosis is an example of device-induced, platelet-mediated arterial thrombosis. Rates of stent thrombosis can vary from <1% to >10% depending on the patient population, genetic predisposition, device type, pharmacological choices, and duration of antiplatelet pharmacotherapy. The Platelet Colloquium is an annual academic–industry–governmental think-tank meeting devoted to identifying research challenges in platelet biology and clinical applications. The latest meeting was held in Washington, DC, on January 25 to 26, 2011, and this review summarizes the discussions of biocompatible stent design, platelet function assessment, and prevention of thrombosis via short- and long-term P2Y12 platelet receptor antagonism.

Stent Design and Surface-Mediated Platelet Activation

The vascular injury induced by percutaneous coronary intervention (PCI) produces dynamic changes on the surface of human platelets.1 Activated platelets are among the first cells to arrive at the site of injury. Stent thrombosis results from the interaction of several procedural, anatomic, and genetically determined factors.2

Early cellular and inflammatory events are influenced by the properties of the stent or its coating. First-generation drug-eluting stents (DES) used relatively thick struts and durable polymers.3 Research efforts focused on development of nonerodable biocompatible materials that could control the release of antiproliferative medications over several weeks.4 In vitro models showed that these devices appeared to be associated with increased platelet activation and adhesion compared with identical bare metal stents (BMS).5 The continuous presence of a durable polymer and drug has been posited to be partly responsible for delayed arterial healing and enhanced stent thrombogenicity.6

Second-generation DES modified some of these components by reducing strut thickness and polymeric drug load.3 In vitro data suggest that the lower polymeric drug load used in current everolimus-eluting stents may have a more favorable thrombogenic profile than BMS controls.7 Recent data also suggest that these devices might favorably affect inflammation and vascular healing after DES implantation.8 In clinical trials, second-generation DES appear to diminish some undesirable biological effects (thrombosis) seen with first-generation DES.9,10 This finding is supported by recent clinical trial data in the setting of ST-segment elevation myocardial infarction, suggesting that everolimus-eluting stents reduce the risk of late stent thrombosis compared with identical BMS controls in this high-risk population (EXAMINATION trial).11

Further research in coating technologies has focused on bioerodable polymeric or polymer-free drug-releasing matrices, potentially allowing the drug-eluting platform to return to its bare metal backbone over several months.12 Several clinical studies have studied the safety and efficacy of third-generation DES using bioabsorbable coatings (Table 1)13–21 and polymer-free platforms (Table 2).22–25 These studies have reported very low rates of late stent thrombosis (LST), while maintaining long-term efficacy.

However, no randomized trial has shown a clear reduction in stent thrombosis with bioabsorbable versus durable polymers. This does not necessarily disprove the concept of durable polymer-induced adverse events; the rates of stent thrombosis may be too low to compare within a randomized trial.18 Thus, although the concept of complete polymer dissolution is attractive, questions about drug bioavailability, degradation profiles, and rebound inflammation remain.

One alternative strategy is to develop a drug elution vehicle that promotes healing and endothelialization. Although anti-CD34–coated stents have been shown to enhance stent coverage in vitro compared with sirolimus-eluting stents,26 several clinical studies using this technology have shown restenosis and LST rates comparable to those with other BMS platforms. Thus, a further step would be to promote endothe-
bialization by fixing antihuman-CD34 antibody to the DES surface.26 In a porcine model of coronary restenosis, anti-
CD34 antibody-coated sirolimus-eluting stents were associated with greater endothelialization at 3 and 14 days, com-
pared with conventional sirolimus-eluting stents.26 However,
a clear clinical benefit of stents coated with this technology has not been shown. A randomized clinical trial using this
dual approach (prohealing and sirolimus elution) is under
development.

Preclinical modeling continues to provide meaningful insights regarding the potential for next-generation DES to
improve clinical outcomes. For example, bench testing of
stent thrombogenicity,7 combined with computational mod-
ing, appears to correlate with clinical outcomes seen in
large randomized trials of second- versus first-generation DES.9,10 If second-generation DES with durable polymers
continue to produce excellent safety profiles, showing the
additional value of newer technologies (ie, polymer free-
coatings) or fourth-generation DES (bioabsorbable polymers
on bioresorbable scaffolds) will become very difficult.

The concept of a fourth-generation, fully bioresorbable
everolimus DES is especially attractive as a potential
way to restore vasomotion and endothelial function to poten-
tially limit any hazard of LST. The challenge will be to show
superiority to second- and third-generation DES with respect to
major adverse cardiovascular events (MACE) or softer end
points (measures of healing or endothelial function).27,28 Based
on likely low rates of clinical events in these future trials,

### Table 1. Balloon-Expandable Stents Using Biodegradable Polymers

<table>
<thead>
<tr>
<th>Stent Type (Manufacturer)</th>
<th>Drug</th>
<th>Stent Material</th>
<th>Polymer Type</th>
<th>Study Type (No. of Patients)</th>
<th>In-Stent Late Loss, mm</th>
<th>Binary Restenosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoStar (Conor Medical)</td>
<td>Paclitaxel</td>
<td>CoCr</td>
<td>PLGA</td>
<td>Randomized controlled trial (CoStar n=989 vs Taxus n=686)</td>
<td>0.64 vs 0.26*</td>
<td>17.9 vs 4.1*</td>
</tr>
<tr>
<td>Supralimus (Sahajanand Medical)</td>
<td>Sirolimus</td>
<td>SS</td>
<td>PLLA PLGA, PLC, PVP</td>
<td>First in man n=100</td>
<td>0.09</td>
<td>0.0</td>
</tr>
<tr>
<td>Excel Stent (JW Medical System)</td>
<td>Sirolimus</td>
<td>SS</td>
<td>PLA</td>
<td>Registry n=2077</td>
<td>0.21</td>
<td>3.8</td>
</tr>
<tr>
<td>NEVO (Cordis)</td>
<td>Sirolimus</td>
<td>CoCr</td>
<td>PLGA Reservoirs</td>
<td>Randomized controlled trial Nevo (n=202 vs PES n=192)</td>
<td>0.13 vs 0.36*</td>
<td>1.1 vs 8.0*</td>
</tr>
<tr>
<td>BioMatrix (Biosensors)</td>
<td>Biolimus A9</td>
<td>SS</td>
<td>Abluminal PLA</td>
<td>Randomized controlled trial BES (n=857 vs SES n=850)</td>
<td>0.13 vs 0.19</td>
<td>20.9 vs 23.3*</td>
</tr>
<tr>
<td>NOBORI (Terumo)</td>
<td>Biolimus A9</td>
<td>SS</td>
<td>Abluminal PLA</td>
<td>Randomized controlled trial BES (n=153 vs PES n=90)</td>
<td>0.11 vs 0.32*</td>
<td>0.7 vs 6.2†</td>
</tr>
<tr>
<td>SYNERGY (Boston Scientific; NICT01135225)</td>
<td>Everolimus</td>
<td>PtCr</td>
<td>PLGA Rollcoat Abluminal</td>
<td>Randomized controlled trial SD vs (LD vs PROMUS Element n=291)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Combo EPC+ drug (OrbusNeich; NCT00967902)</td>
<td>Sirolimus</td>
<td>SS</td>
<td>Abluminal</td>
<td>Randomized controlled trial Combo (stent vs PES; n=180)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Elixir Myolimus (Elixir Medical)</td>
<td>Myolimus</td>
<td>CoCr</td>
<td>Abluminal PLA</td>
<td>First in man n=15</td>
<td>0.15</td>
<td>0</td>
</tr>
<tr>
<td>Infinnium (Sahajanand)</td>
<td>Paclitaxel</td>
<td>SS</td>
<td>PLLA PLGA, PLC PVP</td>
<td>Randomized controlled trial Infinnium (n=111 vs BMS n=57)</td>
<td>0.54 vs 0.90†</td>
<td>8.3 vs 25.5*</td>
</tr>
<tr>
<td>JACTAX Liberté (Boston Scientific)</td>
<td>Paclitaxel</td>
<td>SS</td>
<td>JAC polymer</td>
<td>First in man n=103</td>
<td>0.33</td>
<td>5.2</td>
</tr>
</tbody>
</table>

BES indicates biolimus-eluting stent; BMS, bare metal stent; CoCr, cobalt chromium; EPC, endothelial progenitor cell; JAC, juxtaposed abluminal coating; LD, low
dose; NA, not available; PES, paclitaxel-eluting stent; PL, poly-L-lactide; PLC, 75/25 poly L-lactide-co-caprolactone; PLGA, 50/50 poly DL-lactide-co-glycolide; PLLA,
poly-L-lactic acid; PtCr, platinum chromium; PVP, polyvinyl pyrrolidone; SD, standard dose; SES, sirolimus-eluting stent; SS, stainless steel.

†P<0.001.

### Table 2. Balloon-Expandable Stents Using Polymer-Free DES Platforms

<table>
<thead>
<tr>
<th>Stent Type (Manufacturer)</th>
<th>Drug</th>
<th>Stent Material</th>
<th>Delivery Method</th>
<th>Study Type No. of Patients</th>
<th>In-Stent Late Loss, mm</th>
<th>Binary Restenosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmazoniaPax (Minvasys)</td>
<td>Paclitaxel</td>
<td>CoCr</td>
<td>Abluminal microspray crystallization process</td>
<td>First in man Pax n=16 vs PES n=15</td>
<td>0.77 vs 0.42</td>
<td>NA</td>
</tr>
<tr>
<td>BioFREEDOM (Biosensors)</td>
<td>Biolimus A9</td>
<td>SS</td>
<td>Microporous surface</td>
<td>First in man SD n=25 vs LD n=25 vs PES n=25</td>
<td>0.08 vs 0.37*</td>
<td>NA</td>
</tr>
<tr>
<td>VESTAsync (MIV Therapeutics)</td>
<td>Sirolimus</td>
<td>SS</td>
<td>Nanoporous hydroxyapatite</td>
<td>First in man n=15</td>
<td>0.36</td>
<td>0</td>
</tr>
<tr>
<td>Yukon (Translumina)</td>
<td>Rapamycin</td>
<td>SS</td>
<td>Microporous surface</td>
<td>Randomized controlled trial Yukon n=225 vs PES n=225</td>
<td>0.48 vs 0.48</td>
<td>12.6 vs 11.6</td>
</tr>
</tbody>
</table>

CoCr indicates cobalt chromium; DES, drug-eluting stents; LD, low dose; NA, not available; PES, paclitaxel-eluting stent; SD, standard dose; SS, stainless steel.

†P<0.001.

†P=0.002.
pooling of several randomized studies likely will be needed to evaluate the long-term efficacy and safety of emerging technologies, including the practical question of whether new designs will allow shorter courses of dual antiplatelet therapy (DAPT).

### In Vivo Testing With Platelet Function Assays

Currently, all DES aim to prevent surface-mediated platelet activation through at least 12 months of DAPT—aspirin and a P2Y12 receptor antagonist. Clopidogrel is the most commonly used P2Y12 antagonist, but its pharmacodynamic effects are variable. As a result, various platelet function tests have been proposed to monitor and guide DAPT in this setting. One potential mechanism for limiting the risk of platelet activation and device thrombosis is to individualize the pharmacological approach according to patient-mediated (not device-mediated) risk.

Previous studies in this regard are limited in several important ways. First, the cutoff values derived from the studied populations (primarily at single centers) were not prospectively confirmed in independent validation cohorts. Further, multivariable models showing independent associations between on-treatment reactivity (OTR) while receiving clopidogrel and outcomes were likely “overfitted”; they included too many covariates for too few events. Finally, these studies did not address whether OTR truly is a modifiable risk factor for future cardiovascular events.

Table 3 shows completed and ongoing randomized studies of individualized antiplatelet therapy during or after percutaneous coronary intervention (PCI).

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>n</th>
<th>Population</th>
<th>Intervention</th>
<th>Control</th>
<th>Primary End Point</th>
<th>Follow-Up</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRAVITAS29 (NCT00645918)</td>
<td>2214</td>
<td>Stable CAD/ACS with high OTR to standard clopidogrel after PCI</td>
<td>Clopidogrel 600 mg LD/150 mg MD + ASA</td>
<td>Clopidogrel 75 mg MD + ASA</td>
<td>CV death, non-fatal MI, stent thrombosis</td>
<td>6 mo</td>
<td>HR 1.01 (95% CI: 0.58–1.76); P = 0.97</td>
</tr>
<tr>
<td>TRIGGER-PCI (NCT00910299)</td>
<td>2150</td>
<td>Elective PCI with high OTR to standard clopidogrel</td>
<td>Prasugrel 60 mg loading; then 10 mg daily + ASA</td>
<td>Clopidogrel 75 mg MD + ASA</td>
<td>CV death or MI</td>
<td>6 mo</td>
<td>Stopped for insufficient events after 250 patients completed follow-up</td>
</tr>
<tr>
<td>ARCTIC30 (NCT00827411)</td>
<td>2466</td>
<td>Stable CAD/NSTE-ACS undergoing PCI</td>
<td>Platelet function-guided: P2Y12 reaction units</td>
<td>Conventional: P2Y12 reaction units</td>
<td>Death, MI, stent thrombosis, stroke, or urgent revascularization</td>
<td>12 mo</td>
<td>NA</td>
</tr>
<tr>
<td>TARGET-PCI (NCT01177592)</td>
<td>1500</td>
<td>Nonemergent PCI</td>
<td>Therapy guided by platelet function and/or CYP2C19 genotype</td>
<td>Conventional therapy</td>
<td>CV death, MI, ischemic stroke, urgent revascularization</td>
<td>6 mo</td>
<td>NA</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndromes; ASA, aspirin; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; GPI, glycoprotein IIb/IIIa inhibitor; HR, hazard ratio; LD, loading dose; LOF, loss of function; MI, myocardial infarction; MD, maintenance dose; NA, not available; NSTE, non-ST-segment; OTR, on-treatment reactivity; PCI, percutaneous coronary intervention.

The incidence of MACE at 6 months (primary end point) was 2.3% in both groups (hazard ratio [HR], 1.01; 95% CI, 0.58 to 1.76; P = 0.97).29 Stent thrombosis developed in 0.5% of patients in the higher-dose group and 0.7% of the standard-dose group (P = 0.42). Bleeding rates did not differ significantly, although the proportions of patients with persistently high OTR were modestly but significantly reduced from baseline at 30 days and 6 months.

A separate observational analysis compared GRAVITAS patients assigned to standard-dose clopidogrel after PCI by the presence (n = 1105) or absence (n = 586) of persistently high OTR.31 Patients with high OTR had a nonsignificantly higher rate of MACE than patients without high OTR (HR, 1.68; 95% CI, 0.76 to 3.72; P = 0.20).29 In post hoc analysis, patients with lower levels of OTR after PCI or during follow-up had a significantly lower risk of MACE.31

A more recent trial illustrates the difficulty of showing differences between therapies when event rates are low. In July 2009, the Testing platelet Reactivity In patients undergoing elective stent placement on clopidogrel to Guide alternative thERapy with prasugrel (TRIGGER-PCI; NCT00910299) began enrollment of its 2150 expected patients with stable coronary artery bypass surgery undergoing successful, elective PCI with DES. On March 18, 2011, the sponsor stopped the study after a preliminary, blinded analysis of the first 250 patients to complete follow-up revealed that the trial would not generate enough primary end point events (cardiovascular death or myocardial infarction [MI] at 6 months) for analysis. The study had been designed assuming a 7% incidence of the primary end point for this interval.

Although GRAVITAS did not support treatment with high-dose clopidogrel when 1 platelet function test identified...
high OTR after PCI, it did illustrate some important phenomena. First, OTR was shown to be dynamic for the first month after PCI. Second, the pharmacodynamic effect of the higher maintenance dose was marginal relative to standard dosing in patients with high OTR. Third, the 6-month MACE rate was relatively low with modern DES and techniques used in patients with stable coronary artery bypass surgery. Therefore, very large cohorts will be required to show independent associations between OTR and outcomes, given the multitude of clinical predictors of high OTR and the infrequency of events.

Demonstrating a benefit of antiplatelet therapy tailored to platelet function will be similarly challenging, given the large sample sizes required to provide adequate power to detect outcome differences between treatment groups. Ongoing randomized clinical trials, Thrombocyte Activity Reassessment and GEneTyping for PCI (TARGET-PCI; n = 1500; NCT01177592) and Assessment with a double Randomization of (1) a fixed dose versus a monitoring-guided dose of aspirin and Clopidogrel after DES implantation, and (2) Treatment Interruption versus Continuation, 1 year after stenting (ARCTIC; n = 2500), are likely underpowered in this regard. In addition, given the low event rates observed in stable coronary artery bypass surgery patients, the net clinical benefit of potent P2Y12 inhibitors in patients with high OTR likely will be narrow. Future studies should focus on larger, “enriched” patient populations (eg, acute coronary syndromes) and longer follow-up. For now, the roles of platelet function testing to determine patient-mediated risk and to tailor antiplatelet therapy to prevent platelet-mediated device thrombosis remain unproven.

The American College of Cardiology/American Heart Association guidelines state that physicians may consider platelet function testing to determine platelet inhibitory response in patients receiving thienopyridine therapy if the results of testing might alter management (Class IIb, level of evidence, B). Similarly, the European Society of Cardiology guidelines state that platelet function testing may be considered in selected cases when cilostazol is used (Class IIb, level of evidence, B). Pharmacological Choices and Platelet Activation in DES Thrombosis

In the early stent experience, 5-drug antithrombotic regimens were not uncommon and included aspirin, dipyridamole, dextran, and prolonged heparin followed by warfarin. Despite this intensive therapy, stent thrombosis rates were routinely at or above 5%, with major bleeding rates 2 to 4 times higher. Several randomized trials showed substantial decreases in thrombotic complications with aspirin plus thienopyridine therapy versus either aspirin alone or aspirin plus warfarin (Figure 1). These studies highlighted the critical role of using inhibitors of platelet activation (aspirin and P2Y12 receptor antagonists) to prevent stent thrombosis. The fact that DAPT not only was a more effective antithrombotic but also significantly reduced bleeding risk compared with a warfarin-based regimen is an important lesson; there needs to be a tradeoff of increased bleeding for improved thrombosis prevention when the correct thrombotic pathway is targeted.

Platelet activation occurs almost immediately after stenting and appears to peak ~2 to 4 hours afterward. In addition to aspirin, platelet P2Y12 antagonists have been the primary agents used to minimize platelet activation. Although clopidogrel has been the gold standard, it has several limitations. Specifically, it was never designed to maximize inhibition of the platelet P2Y12 receptor; in fact, it is thought to routinely inhibit only ~80% of the ~800 P2Y12 receptors on the platelet surface. In contrast, the newer thienopyridine prasugrel and the nonthienopyridine ticagrelor were specifically designed to achieve higher levels of inhibition. These agents appear to block 100% of platelet surface P2Y12 receptors.

This enhanced antiplatelet effect is likely explained by the more efficient generation of prasugrel’s active metabolite compared with clopidogrel’s. Similarly, ticagrelor is a nonthienopyridine P2Y12 receptor antagonist with greater potency and more rapid achievement of therapeutic levels compared with clopidogrel. The platelet inhibition and patient outcomes trial showed a significant 16% reduction in the primary end point (death from vascular causes, MI, or stroke) and reductions in stent thrombosis and all-cause mortality with ticagrelor compared with clopidogrel.
in patients with acute coronary syndromes. Prasugrel and ticagrelor have different pharmacokinetics and side effect profiles, but both agents increase non-coronary artery bypass surgery related bleeding compared with clopidogrel. The benefit of both prasugrel and ticagrelor with respect to prevention of stent thrombosis has led to US (prasugrel) and European (ticagrelor and prasugrel) Class I guideline recommendations for these more potent agents. Thus, the clinical trial data are consistent with the concept that higher levels of P2Y₁₂ inhibition translate into greater protection from thrombotic events compared with clopidogrel.

Clinical trials of newer P2Y₁₂ inhibitors and novel inhibitors of other platelet thrombin receptors (such as protease activated receptor-1) offer the possibility of enhanced inhibition of platelet activation in various clinical scenarios. Cangrelor and elinogrel are both intravenous nonthienopyridine P2Y₁₂ inhibitors (elinogrel also has an oral form). In vitro and ex vivo data show that they provide high levels of inhibition against adenosine diphosphate-induced platelet aggregation, but Phase 3 trials of cangrelor were disappointing. Elinogrel is now entering Phase 3 study, after earlier clinical trials showed promising results. Protease activated receptor-1 inhibitors offer a novel mechanism for minimizing platelet activation with encouraging Phase 2 data, but definitive Phase 3 data have yet to be published.

### Blocking Platelet-Mediated Thrombosis Over the Long Term

Although devices, pharmacological therapies, patient testing strategies, and development have focused on the general prevention of device-mediated thrombosis, the specific issue of LST has been most readily addressed by extending the duration of PCI pharmacotherapies. Whether new biocompatible/nondurable polymer DES will obviate this need remains to be determined. For the immediate future, the question is not whether extended DAPT is needed to prevent late platelet-mediated thrombosis, but for how long.

Early studies of sirolimus-eluting stents and paclitaxel-eluting stents mandated 2 or 6 months of DAPT. In 2006, however, registry data raised concern about the risk of LST-related death and MI. A prospective cohort study also had identified premature DAPT discontinuation as an independent predictor of stent thrombosis within the first 9 months among 2229 patients who had been prescribed DAPT for 3 to 6 months after DES implantation. Another large cohort study reported that LST can occur at an annual rate of 0.6% up to 3 years after DES implantation. Long-term concern about LST has been highlighted by findings from the recent Sirolimus-eluting versus paclitAXel-eluting stents for coronary revascularization (SIRTaX) LATE trial, in which the annual rate of stent thrombosis was 0.65% between 1 and 5 years after implantation of first-generation DES.

### Table 4. Registries Assessing Outcomes Relative to DAPT Adherence

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Population</th>
<th>Study Duration</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airoldi</td>
<td>3021</td>
<td>DES</td>
<td>18 mo</td>
<td>DAPT protective for ST only during first 6 mo; median time to ST with DAPT cessation &lt;6 mo = 14 d; 90 d thereafter</td>
</tr>
<tr>
<td>Park</td>
<td>2873</td>
<td>Event-free DES</td>
<td>3 y</td>
<td>No reduction in death, MI, ST with DAPT after 1 y</td>
</tr>
<tr>
<td>j-Cypher</td>
<td>10 778</td>
<td>SES</td>
<td>2 y</td>
<td>Discontinuation of DAPT, but not of aspirin alone, associated with ST at any time points</td>
</tr>
<tr>
<td>Schulz</td>
<td>6816</td>
<td>DES</td>
<td>4 y</td>
<td>DAPT protective for ST only during first 6 mo; median time to ST with DAPT discontinuation &lt;6 mo = 9 d; 104 d thereafter</td>
</tr>
<tr>
<td>Roy</td>
<td>2889</td>
<td>DES</td>
<td>1 y</td>
<td>DAPT not protective for ST after 6 mo</td>
</tr>
<tr>
<td>Van Werkum</td>
<td>21 009</td>
<td>DES, BMS</td>
<td>30.9 mo</td>
<td>ST associated with DAPT discontinuation within 1 y; risk greatest if discontinued &lt;30 d</td>
</tr>
<tr>
<td>Petersen</td>
<td>9256</td>
<td>DES</td>
<td>1 y</td>
<td>Prolonged DAPT use associated with greater bleeding risk but lower risk of death or nonfatal MI</td>
</tr>
<tr>
<td>e-SELECT</td>
<td>15 147</td>
<td>SES</td>
<td>1 y</td>
<td>ST associated with any DAPT discontinuation within 30 d</td>
</tr>
</tbody>
</table>

BMS indicates bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stents; MI, myocardial infarction; ST, stent thrombosis.
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Finally, type and duration of DAPT therapies are not the only issues pertaining to this debate; bleeding risk and anti-thrombotic benefits of DAPT might vary according to aspirin dose\(^{63,74}\) or regional variations in care.\(^{75}\) Once we reach 2014, will we no longer need to rely on postapproval surveillance data and registry studies to determine the optimal duration of DAPT to prevent coronary stent thrombosis? This seems unlikely; pharmacological agents, polymers, stent designs, and practice patterns continue to evolve far more rapidly than does the randomized evidence. It is unlikely that we can perform 20,000-patient clinical trials for each new generation of DES, and it might be false to assume a class effect with respect to device-mediated thrombosis. Thus, preclinical testing and assessment of patient-related risk will continue to be critical. Well-organized registries can continue to offer useful information in this regard, keeping in mind the observational nature of the data collected.

Conclusions

In summary, stent thrombosis cannot be viewed from a singular device, patient, or pharmacological perspective; prevention of platelet-mediated stent thrombosis requires a 3-fold approach focusing on the development of improved polymer systems, assessment of individual patient-related platelet pathophysiology, and optimization of the dose and duration of platelet receptor antagonist therapy:

- Stent thrombosis is an example of acute and delayed device-induced, platelet-mediated device thrombosis.
- Emerging DES platforms are moving toward biocompatible and bioerodable polymers, which aim to prevent potential platelet activation and inflammation associated with early earlier-generation DES designs.
- Although comparative clinical trials will provide an important evidence base, distinguishing the potential advantages of iterative changes in DES design will likely hinge on in vitro testing methods, soft end points (stent healing, endothelial function), and well-designed registry analyses.
- The scientific community still faces the challenges of treating patient-specific risks of platelet-mediated stent thrombosis with point-of-care testing.
- DAPT focusing on P2Y\(_{12}\) receptor antagonism has a proven role in preventing platelet-mediated stent thrombosis. The role of newer agents in preventing stent thrombosis is proven, but the optimum treatment duration of DAPT therapy remains uncertain.

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References


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Supplemental Material

Appendix. Participants in the 2011 Platelet Colloquium

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